Treatment with LY2409021, a Glucagon Receptor Antagonist, Increases Liver Fat in Patients with Type 2 Diabetes

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Short title: Phase 2b Results for LY2409021

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Abstract

Aims

Glucagon receptor antagonists (GRAs) represent a clinically validated new class of molecules for the treatment of type 2 diabetes (T2D) however these molecules are associated with increases in hepatic aminotransferases. We evaluated whether treatment with LY2409021, a novel, selective GRA, is associated with changes in hepatic fat and other safety parameters related to the benefit-risk profile for chronic use.

Materials and Methods

Safety and efficacy were assessed in patients with T2D taking metformin and sulfonylurea randomized to LY2409021 20mg (N=65), placebo (N=68), or sitagliptin 100mg (N=41). Key

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endpoints included change from baseline to Month 6 in hepatic fat fraction (HFF) by magnetic resonance imaging, hepatic aminotransferases, blood pressure (BP), lipid profile, fasting plasma glucose (FPG), and hemoglobin A1c (HbA1c).

Results

Significant increase in HFF was seen with LY2409021 versus sitagliptin (least squares mean difference: 3.72%; $p<0.001$) and placebo (4.44%; $p<0.001$), accompanied by significant alanine aminotransferase elevations with LY2409021 versus sitagliptin (6.8U/L; $p=0.039$) and placebo (10.7U/L; $p<0.001$). No patients had concomitant elevations in bilirubin. LY2409021 treatment showed significant HbA1c reductions versus placebo (least squares mean difference: -0.77%; $p<0.001$) but not sitagliptin (-0.20%; $p=0.383$). Similar results were observed for FPG. LY2409021 was also associated with significant increases in systolic BP versus sitagliptin (4.9 mmHg; $p=0.030$) and placebo (4.3 mmHg; $p=0.029$) as well as significant increases in body weight and total cholesterol. All effects of LY2409021 were reversible.

Conclusion

In this T2D cohort, chronic glucagon receptor antagonism with LY2409021 was associated with glucose lowering but also demonstrated increases in hepatic fat, hepatic aminotransferases, and other adverse effects.

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Introduction

Glucagon, a 29-amino-acid peptide released from the α-cells of the islet of Langerhans, plays a key role in glucose homeostasis.[1,2] Glucagon action is transduced by the class B G-protein-coupled glucagon receptor (GCGR), located on liver, kidney, intestinal smooth muscle, brain, adipose tissue, heart, and pancreas cells.[1,2] After carbohydrate ingestion in healthy individuals, glucagon secretion is suppressed, reducing glucagon-induced stimulation of hepatic glucose production.[3] The pathophysiology of type 2 diabetes mellitus (T2D) is characterized not only by insulin resistance and beta cell dysfunction but also by hyperglucagonemia in the fasting state and abnormal glucagon suppression after a meal.[4] Administration of recently identified small-molecule GCGR antagonists in patients with T2D results in a substantial reduction of fasting and postprandial glucose concentrations and has made antagonism of the glucagon receptor an attractive target for the treatment of T2D.[3] In addition to its effects on carbohydrate metabolism, glucagon is known to exert effects on lipid metabolism, including promoting fatty acid oxidation in hepatocytes.[5]

LY2409021 is a novel agent that competitively blocks the GCGR. It has a long half-life (approximately 60 hours) and is administered orally once daily. While several studies with LY2409021 have demonstrated significant glycaemic lowering effect in patients with T2D, results have also shown dose-dependent and reversible increases in hepatic aminotransferase levels.[6] The current study was designed to further assess the risk-benefit profile of LY2409021 and to investigate the mechanism underlying the increases in hepatic aminotransferases and assess their correlation with changes in hepatic fat.

Materials and Methods

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Study design and patients

This Phase 2b, randomised, double-blind, placebo- and active comparator-controlled study (ClinicalTrials.gov NCT02111096) was conducted at 35 study centers in 3 countries in accordance with regulatory standards of good clinical practice, the Declaration of Helsinki, and all applicable local regulations. The protocol was approved by each site's ethical review board. All patients provided written informed consent before initiation of study procedures.

Patients were male or female, ≥18 and <80 years old, with a diagnosis of T2D[7] who were on an optimally effective and stable dose of metformin and a sulfonylurea; had hemoglobin A1c (HbA1c) values ≥7.0% and ≤10.0%; and a body mass index (BMI) ≥20 and <40 kg/m^2. Main exclusion criteria included hepatitis B, hepatitis C, or clinical signs/symptoms of liver diseases; hepatic aminotransferases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) >2x upper limit of normal (ULN); elevated alkaline phosphatase (>ULN) unrelated to bone metabolic disease; elevated total bilirubin level (>ULN); history of multiple endocrine neoplasia; systolic blood pressure (SBP) >160 mm Hg or diastolic blood pressure (DBP) >90 mm Hg; current use of systemic glucocorticoid therapy, amiodarone, methotrexate, isoniazid, or tamoxifen; and an average weekly alcohol intake that exceeds 2 units per day for males and 1 unit per day for females. Full inclusion and exclusion criteria can be found in a Supplementary Appendix.

This study was originally designed with primary endpoint after 6 months of treatment and a total treatment period of 12 months. However, the decision to terminate early was made based on results from a dedicated ambulatory blood pressure monitoring study, which showed an increase in blood pressure with LY2409021 treatment.[8] The sponsor made the determination that the

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overall risk-benefit profile of LY2409021 was unlikely to support its use as a chronic treatment for T2D. At that time, investigators in the current study were instructed to take their patients off study medication and complete the 4-month posttreatment safety follow-up visit.

Randomisation and masking

Patients who met all criteria for enrollment were randomised to double-blinded LY2409021, placebo, or sitagliptin in a 3:3:2 ratio by a computer-generated random sequence procedure. Stratification was based upon country and baseline HbA1c level (≤8.0%, >8.0%). Participants, caregivers, and study personnel were masked to treatment assignment. Members of an independent Assessment Committee had access to unmasked data reports but had no contact with study sites or participants.

Procedures

The study consisted of a 1-week screening period, a 2-week lead-in period, and a 12-month placebo- and active-control period, followed by a 4-month posttreatment safety follow-up period and an additional 6-month posttreatment safety follow-up visit, if needed. Investigational product (LY2409021 20 mg, placebo, or sitagliptin 100 mg) was administered orally once daily. The dose of LY2409021 was selected on the basis of the safety and efficacy profile of LY2409021 demonstrated in previous Phase 2 studies. Insulin was allowed as rescue therapy based on pre-specified fasting glucose or HbA1c criteria.

Liver fat content was assessed as hepatic fat fraction (HFF) measured by noncontrast magnetic resonance imaging (MRI). Each baseline MRI was quality reviewed and approved by the core imaging laboratory before randomising the patient. MRIs performed at baseline, 1, 3, 6, and 12 months from first treatment dose; at early discontinuation (if applicable); and at 4 months

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posttreatment were used to characterize the extent, time course, and reversibility of changes in HFF. Full details for MRI are provided in a Supplementary Appendix.

Fasting samples for plasma glucagon were taken in duplicate and analysed using a novel high-sensitivity electrochemiluminescence sandwich immunoassay.[9] Other clinical chemistry endpoints were measured using commercially validated methods; LDL cholesterol was calculated with the Friedewald formula. Anthropometry was completed according to standard procedures; blood pressure and pulse were recorded in triplicate throughout the study. Self-monitoring of blood glucose and glucose levels at study visits were used to determine episodes of hypoglycaemia.

Outcome measurements

The primary outcome of this study was to compare LY2409021 to placebo on the liver fat change from baseline to Month 6. Key secondary outcomes of the study were to compare LY2409021 to sitagliptin on the HFF change from baseline to Month 6 and Month 12 as well as comparisons of LY2409021 to placebo and to sitagliptin on the following parameters: hepatic aminotransferases, HbA1c, fasting plasma glucose, fasting glucagon, fasting lipids, vital signs, body weight, and hypoglycaemia incidence.

Statistical analysis

Sample size determination was based upon the comparison of LY2409021 treatment arm with placebo in the change in HFF to Month 6. Approximately 60 patients per arm were needed to achieve >90% power to detect a treatment difference of 6%, assuming a standard deviation (SD) of 8%, a 20% dropout rate, and 25% of patients without a usable HFF measure at the 6-month visit.[10]

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Analysis of the primary endpoint was based upon a modified intent-to-treat population defined as all randomised patients who received at least 1 dose of study drug and had a usable baseline HFF and at least 1 usable postbaseline measure. Efficacy and other safety analyses were conducted on the intent-to-treat population defined as all randomised patients who received at least 1 dose of randomised study drug.

The primary and key secondary outcome analyses were conducted for the 6-month treatment period excluding data after use of rescue therapy. Other safety analyses included all data regardless of rescue therapy or use of investigational product unless otherwise specified. Due to early termination of the trial, limited data are available for the 12-month treatment period; therefore, only summary data for HFF and hepatic aminotransferases are presented for Month 12.

Continuous efficacy and safety variables measured repeatedly were analysed using a mixed-model repeated measures model that consisted of baseline as a covariate and pooled country, baseline HbA1c stratum (≤8.0%, >8.0%, excluded from the analysis model for HbA1c), treatment, visit, and visit-by-treatment interaction as fixed effects. Least squares mean estimates of each treatment and its 95% confidence interval were reported together with p-values of the treatment comparisons of LY2409021 versus placebo and versus sitagliptin.

Hypoglycaemia incidence, excluding data after use of rescue therapy, was analysed with a Cochran-Mantel Haenszel test stratified by baseline HbA1c (≤8.0%, >8.0%). A chi-square or Fisher's exact test was used for pair-wise comparisons of other adverse events (AEs).

Correlation coefficients and p-values based upon Spearman rank test were summarized for change from baseline in HFF versus the following change from baseline values: ALT, AST,

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alkaline phosphatase, gamma-glutamyltransferase (GGT), total bilirubin, indirect bilirubin, direct bilirubin, fasting lipids, fasting glucagon, HbA1c, and BMI.

Results

Patient disposition and baseline characteristics

A total of 174 patients were randomly assigned to treatment: LY2409021 n=65, placebo n=68, and sitagliptin n=41 (Figure S1). The treatment groups were mostly well-balanced with regard to demographics and baseline characteristics (Table 1). A total of 132 patients completed 6 months (primary endpoint of the study). Median exposure was 242 days for LY2409021, 225 days for placebo, and 251 days for sitagliptin.

Outcomes

Hepatic safety

The majority of patients had steatosis at baseline (HFF >5.5% [11]). Mean of each group was 11% to 15% but individual patients had baseline HFF as low as 1.3% and as high as 42%. At Month 6, treatment with LY2409021 resulted in a statistically significant increase in HFF compared to placebo and sitagliptin (Figure 1A). Mean HFF returned to baseline or near baseline levels by 4 months posttreatment in all treatment groups. Figure 1B shows that across all time points through Month 6, a numerically greater proportion of patients in the LY2409021 arm fell into categories with larger HFF increases compared to placebo and sitagliptin.

At Month 6, treatment with LY2409021 resulted in a statistically significant increase in ALT compared to placebo and sitagliptin (Figure 2). Changes in AST levels were significantly increased for LY2409021 compared to placebo (7.1 U/L vs -0.4 U/L; p=0.002) but not sitagliptin

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(7.1 U/L vs 4.8 U/L; p=0.391). No patient had concomitant elevations in ALT/AST and bilirubin. Mean ALT and AST values returned to baseline or near baseline levels by 4 months posttreatment. No statistically significant changes in mean total bilirubin, GGT, or alkaline phosphatase were seen between treatments at Month 6.

Glycaemic-related efficacy measurements

At Month 6, there was a statistically significant reduction in HbA1c for the LY2409021 treatment group compared to placebo but not sitagliptin (Figure 3). Similar results were observed for fasting plasma glucose (see Supplementary Appendix). In addition, a statistically significantly higher percentage of patients attained HbA1c targets of ≤6.5% and <7% in the LY2409021 group compared to placebo and sitagliptin (see Supplementary Appendix). During 6 months of treatment, 5 patients (2.9%) initiated insulin as rescue therapy (LY2409021: 1 patient [1.5%]; sitagliptin: 1 patient [2.4%]; placebo: 3 patients [4.4%]).

Other laboratory measurements: glucagon and lipids

At Month 6, LY2409021 treatment resulted in a statistically significant mean increase from baseline in glucagon compared to sitagliptin and placebo (44.06 pmol/L vs 3.38 pmol/L and 5.05 pmol/L, respectively; p<0.001 for both). Treatment with LY2409021 also resulted in statistically significant increases in glucagon over sitagliptin and placebo at Month 1 and Month 3 (p<0.001 for all). At 4 months posttreatment, mean glucagon levels had returned to or were near baseline levels in all groups: pmol/L mean (SD); LY2409021: 20.4 (9.9), sitagliptin: 20.6 (9.4); placebo: 16.1 (8.4).

Figure S2 shows the change from baseline to Month 6 in lipid parameters. At Month 6, the mean increase from baseline for total cholesterol was statistically significantly greater in the

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LY2409021 group compared to sitagliptin (0.468 vs 0.006 mmol/L; p=0.004) and placebo (0.468 vs 0.130 mmol/L; p=0.016). Mean total cholesterol values returned to baseline or near baseline levels by 4 months posttreatment. A statistically significant increase in low density lipoprotein was also observed for LY2409021 compared to sitagliptin at Month 6 (0.244 vs -0.075 mmol/L; p=0.028) but not compared to placebo. No significant differences were observed across treatment arms for high density lipoprotein or triglycerides.

Hemodynamic effects

At Month 6, a statistically significant increase in SBP was observed in the LY2409021 treatment group compared to sitagliptin and placebo (Figure 4A). LY2409021 also had numerically greater, but not statistically significant, DBP increase compared to sitagliptin and placebo (Figure 4B). At 4 months posttreatment, mean SBP and DBP had returned to or were near baseline levels in all groups. There were no statistically significant treatment differences in change from baseline to Month 6 for pulse rate.

Anthropometric effects

A statistically significant increase in weight was observed at Month 6 for LY2409021 compared to sitagliptin (1.16 vs -0.23 kg; p=0.007]) and placebo (1.16 vs -0.08 kg; p=0.006) (Figure S3). At 4 months posttreatment, mean weight had returned to or was near baseline levels in all groups.

Correlations

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Changes in HFF were positively correlated with changes in ALT ($p<0.001$) and AST ($p<0.001$) for LY2409021; a positive correlation between HFF and ALT was also observed for placebo ($p=0.038$).

For LY2409021, changes in HFF were not significantly correlated with changes in fasting plasma glucagon or total cholesterol. In addition, changes in fasting plasma glucagon were not correlated with changes in vital signs for LY2409021

Adverse events

A serious AE of hypertensive crisis, not related to study treatment, was reported in an LY2409021-treated patient. There were no liver-related serious AEs. Additional AE data are included in Supplementary Appendix.

Total hypoglycaemia incidence through Month 6 was significantly higher with LY2409021 than placebo (48.4% versus 19.1%; $p<0.001$) but similar to sitagliptin (48.4% versus 47.5%; $p=0.993$). There were no events of severe hypoglycaemia in any group.

Discussion

Inhibition of glucagon action represents a clinically validated new approach to reduction of hyperglycaemia and a compelling therapeutic option for T2D.[12,13] There are currently several molecules in different stages of clinical development that target the inhibition of glucagon action including small molecule antagonists, human antibodies, and antisense oligonucleotides (ISIS-GCGRRx [Ionis], LGD-6972 [Ligand], PF-06291874, PF-06293620 [Pfizer], REMD-477 [REMD Biotherapeutics]).[14-19] Some of the benefits that have made the glucagon receptor antagonist (GRA) class so attractive as a therapeutic target are the low risk of hypoglycaemia

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and moderate to strong glycaemic control. IONIS reported a remarkable 2.25% reduction in HbA1c over 11 weeks of treatment with their molecule ISIS-GCGRx.[14] Further enthusiasm from a recent publication expressed treatment for type 1 diabetes as an exciting direction underexplored for GRAs.[19] Based on our results, excitement for this class may be premature.

There are drawbacks with antagonism of GCGR. The most common side effect reported with GRA therapy is hepatic aminotransferase elevation.[15-17, 20-22] Another potential concern is malignant transformation of alpha cells as they undergo marked hyperplasia when the action of their secretory product is blocked.[19] In fact, the clinical development of 2 GRAs, BAY 27-955 and MK-0893, has been abandoned[23]; for MK-0893, side effects including hypertension, elevated aminotransferases, weight gain, and unfavorable changes in lipid profile have been reported.[20,21]

The findings in this study included significant hepatic fat accumulation and an increase in blood pressure on a background of persistent hepatic aminotransferase elevations in patients exposed to LY2409021. Increases in total cholesterol and body weight were also observed. These effects have not been previously demonstrated with LY2409021 treatment but some have been reported, together with hepatic aminotransferase elevations, for MK-0893 and PF-06291874[16,20,21] suggesting that such changes may be related to the mechanism itself.

The mechanism behind HFF accumulation and increases in hepatic aminotransferase levels during GRA treatment is unclear. Glucagon exerts multiple hypolipidemic actions directly on hepatocytes in part through a PPARα-dependent pathway.[13] Studies have shown that high fat feeding of GCGR-/- mice was associated with accelerated development of steatosis in some but not all studies.[13] The findings in animals involving multiple GCGR -/- species together with

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novel results from this study in humans imply that a threshold level of GCGR signaling is required for hepatocytes to regulate synthesis, secretion, and oxidation of lipids, and marked attenuation of GCGR signaling would be predicted to be associated with an increased risk of dyslipidemia and fatty liver. Although reversible after treatment discontinuation, significant HFF increase with elevations in hepatic aminotransferases are unwanted side effects for long-term treatment of patients with T2D, a population already at risk of non-alcoholic fatty liver disease.[24]

Elevations in blood pressure observed for LY2409021 support findings from a separate ambulatory blood pressure monitoring study with LY2409021.[8] Moreover, increases in blood pressure have also been observed with MK-0893 and PF-06291874.[16,21] This suggests that, in addition to elevations in hepatic aminotransferases, elevations in blood pressure may be an untoward side effect in common with this class of molecules.

Consistent with weight gain reported with MK-0893,[20] LY2409021 is the second GRA to demonstrate an increase in body weight, although not always observed in other studies.

One limitation of the current study was the early termination of the trial that prevented the collection and analysis of the complete 12-month data. Also, the lack of liver biopsies precludes meaningful conclusions regarding the development of steatohepatitis[25,26] or other histologic evidence of liver injury. Nonetheless, we believe that this well powered study which longitudinally evaluated multiple safety and efficacy endpoints versus placebo and active comparator provides a robust assessment of the benefit-risk profile of LY2409021.

Although alpha cell hyperplasia has been identified as a potential long-term treatment concern for GRAs,[19] our results show other safety side effects that can manifest as early as 1 month after treatment initiation. Data from this trial recapitulate findings from other trials with different

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GRAs and show for the first time that this mechanism is associated with significant hepatic fat accumulation along with elevations in hepatic aminotransferases, blood pressure, lipid parameters, and body weight. Taken together, although this mechanism may carry appeal for its glucose lowering efficacy, some of the attendant adverse effects raise questions regarding the suitability of glucagon receptor antagonism as a chronic treatment for T2D.

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Contributors: CBG, RL, TAH, CK were involved in the development of the clinical protocol. CBG and XMZ were involved in the oversight of patient safety during the clinical trial. CBG and XMZ were involved in the analysis and interpretation of the data, critically revised the manuscript for important intellectual content and scientific significance, and assisted with drafting and supervising the development of the manuscript. RL was involved in the statistical analysis and interpretation of the data and critically revised the manuscript for important intellectual content. AR, SS, PG, SGP, CK, TAH, and NC were involved in the interpretation of the data and critically revised the manuscript for important intellectual content and scientific significance. All authors approved the final version of the manuscript.

Declaration of interest: CBG, XMZ, RL, AR, SS, PG, SGP, CK, and TAH are employees of Eli Lilly and Company. NC is consultant for AbbVie Inc, Eli Lilly and Co, Tobira Therapeutics, Takeda Pharmaceutical Co, NuSirt Biopharma, and DS Biopharma; and has received research support from Gilead Sciences Inc, Galectin Therapeutics, Eli Lilly and Co, and Intercept Pharmaceuticals.

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Table 1. Summary of Demographics and Baseline Characteristics

Variable	LY2409021 (N = 65)	Sitagliptin (N = 41)	Placebo (N = 68)	Total (N = 174)
Sex, Male, n (%)	41 (63.1)	31 (75.6)	37 (54.4)	109 (62.6)
Age, years, mean (SD)	56.9 (8.3)	57.1 (9.0)	57.8 (8.2)	57.3 (8.4)
Age group, <65 years, n (%)	54 (83.1)	33 (80.5)	55 (80.9)	142 (81.6)
Ethnicity, n (%)				
Not Hispanic or Latino	34 (52.3)	21 (51.2)	25 (36.8)	80 (46.0)
Hispanic or Latino	30 (46.2)	19 (46.3)	42 (61.8)	91 (52.3)
Not Reported	1 (1.5)	1 (2.4)	1 (1.5)	3 (1.7)
Race, n (%)				
Caucasian	42 (64.6)	31 (75.6)	51 (75.0)	125 (71.3)
Asian	4 (6.2)	2 (4.9)	5 (7.4)	11 (6.3)
African American	14 (21.5)	6 (14.6)	11 (16.2)	31 (17.8)
Multiple	5 (7.7)	2 (4.9)	1 (1.5)	8 (4.6)
Weight, kg, mean (SD)	94.2 (22.5)	94.0 (20.9)	85.7 (17.9)	90.8 (20.7)
BMI, kg/m^2, mean (SD)	32.6 (5.5)	31.8 (6.1)	31.2 (4.9)	31.8 (5.4)
Duration of diabetes, years, mean (SD)	12.4 (6.3)	10.9 (6.5)	10.2 (6.3)	11.2 (6.4)
HbA1c, %, mean (SD)	8.1 (1.0)	8.3 (0.9)	8.3 (0.9)	8.2 (0.9)
HbA1c >8%, n (%)	29 (44.6)	19 (46.3)	38 (55.9)	86 (49.4)
Fasting plasma glucose, mmol/L, mean (SD)	9.17 (2.34)	9.79 (2.85)	9.38 (2.50)	9.40 (2.53)
Fasting plasma glucagon, pmol/L, mean (SD)[a]	16.5 (8.3)	17.2 (10.1)	12.8 (5.6)	15.2 (8.1)
HFF, %, mean (SD)	12.98 (8.54)	14.75 (9.38)	11.47 (8.78)	12.79 (8.87)

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ALT, U/L, mean (SD)	28.1 (14.4)	31.6 (19.7)	23.9 (14.1)	27.3 (15.9)
AST, U/L, mean (SD)	23.7 (13.4)	26.0 (13.5)	20.1 (8.5)	22.8 (11.9)
Cholesterol, mmol/L, mean (SD)	4.54 (0.96)	4.67 (0.85)	4.67 (1.10)	4.62 (0.99)
Triglycerides, mmol/L, mean (SD)	2.04 (1.25)	2.01 (0.96)	1.87 (0.90)	1.97 (1.05)
LDL-C, mmol/L, mean (SD)	2.44 (0.87)	2.55 (0.68)	2.61 (0.97)	2.53 (0.87)
HDL-C, mmol/lL, mean (SD)	1.19 (0.30)	1.20 (0.26)	1.24 (0.31)	1.21 (0.30)
Systolic BP, mm Hg, mean (SD)	126.4 (13.3)	128.2 (11.4)	125.8 (12.3)	126.6 (12.5)
Diastolic BP, mm Hg, mean (SD)	76.8 (6.7)	75.7 (7.3)	76.0 (7.9)	76.2 (7.3)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BP = blood pressure; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; HFF = hepatic fat fraction; LDL-C = low-density lipoprotein cholesterol; n = number of patients; N = number of patients in population; SD = standard deviation.
[a]Normal range: 1.7 to 24.5 pmol/L[9]

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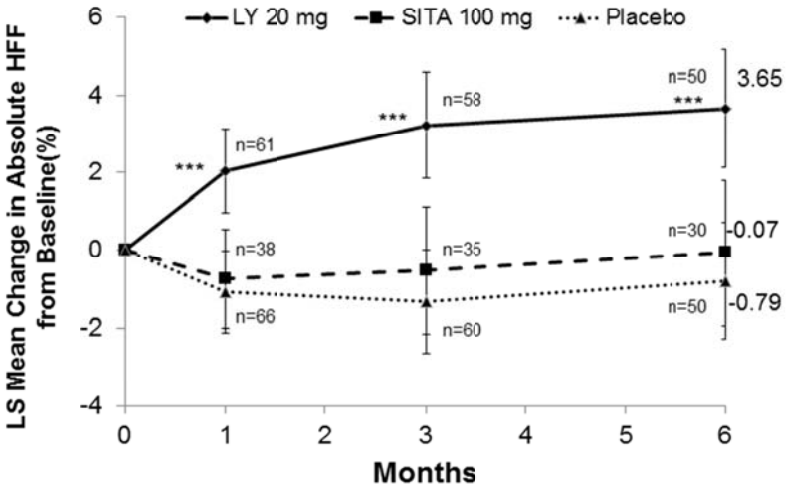
Figure 1A. Hepatic Fat Fraction: Change from Baseline to Month 6[a]



***p<0.001 LY vs. placebo and LY vs. sitagliptin

HFF, %	LY2409021		Sitagliptin		Placebo	
	n	mean (SD)	n	mean (SD)	n	mean (SD)
Baseline	62	12.98 (8.54)	39	14.75 (9.38)	67	11.47 (8.78)
Month 6	50	17.16 (9.77)	30	14.74 (9.53)	50	11.07 (8.23)
Month 12	14	16.18 (8.61)	4	18.83 (4.71)	10	10.09 (8.92)
4 months posttreatment	58	12.24 (7.50)	35	13.26 (8.89)	54	11.36 (8.29)

[a] The primary endpoint of the study was Month 6.

Abbreviations: HFF = hepatic fat fraction; LS = least square; LY = LY2409021; n = number of patients; SD = standard deviation; SITA = sitagliptin.

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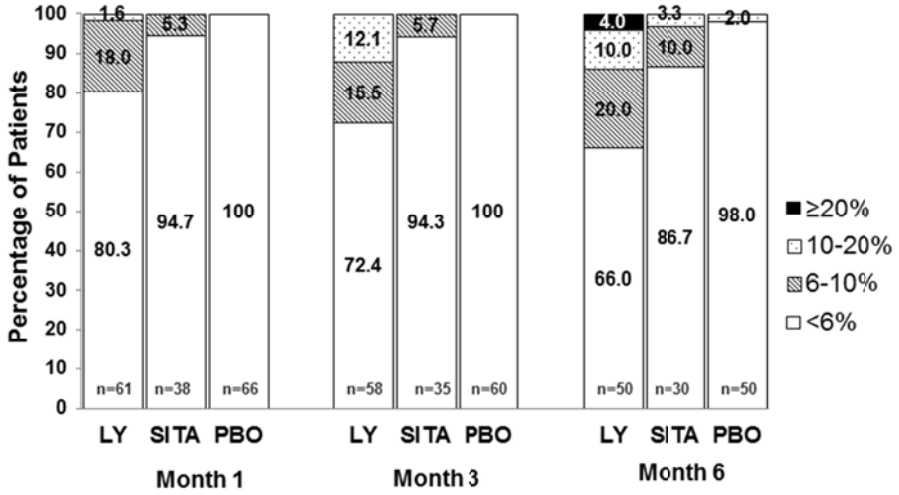
Figure 1B. Categorical Analysis of HFF Change from Baseline through Month 6[a]



[a] The primary endpoint of the study was Month 6.

Abbreviations: HFF= hepatic fat fraction; LY = LY2409021; PBO = placebo; n = number of patients; SITA = sitagliptin.

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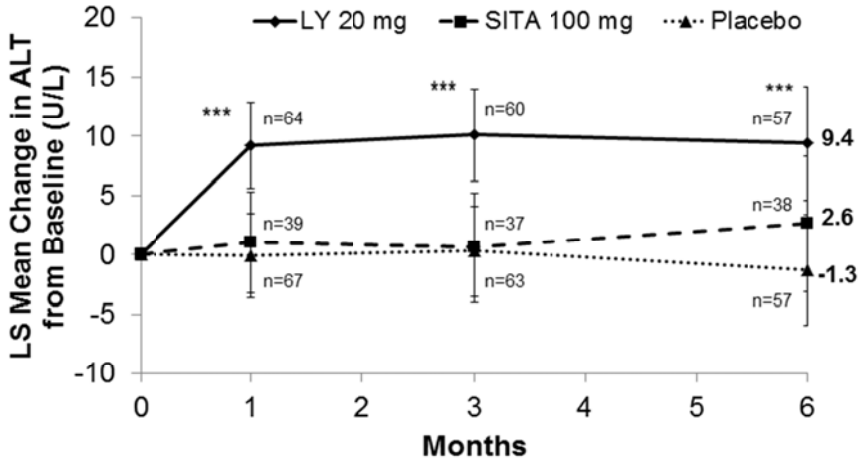
Figure 2. Alanine Aminotransferase: Change from Baseline to Month 6[a]



***p<0.001 LY vs. placebo; p<0.001 LY vs. sitagliptin at Months 1 and 3, p<0.05 LY vs. sitagliptin at Month 6

ALT, U/L	LY2409021		Sitagliptin		Placebo	
	n	mean (SD)	n	mean (SD)	n	mean (SD)
Baseline	65	28.1 (14.1)	41	31.6 (19.7)	68	23.9 (14.4)
Month 6	57	36.0 (21.8)	38	31.1 (29.4)	57	22.2 (11.7)
Month 12	24	32.0 (16.8)	15	26.2 (12.3)	19	27.2 (18.0)
4 months posttreatment	57	27.8 (13.3)	37	28.5 (18.6)	57	23.9 (15.1)

[a] The primary endpoint of the study was Month 6.

Abbreviations: ALT = alanine aminotransferase; LS = least square; LY = LY2409021; n = number of patients; SITA = sitagliptin.

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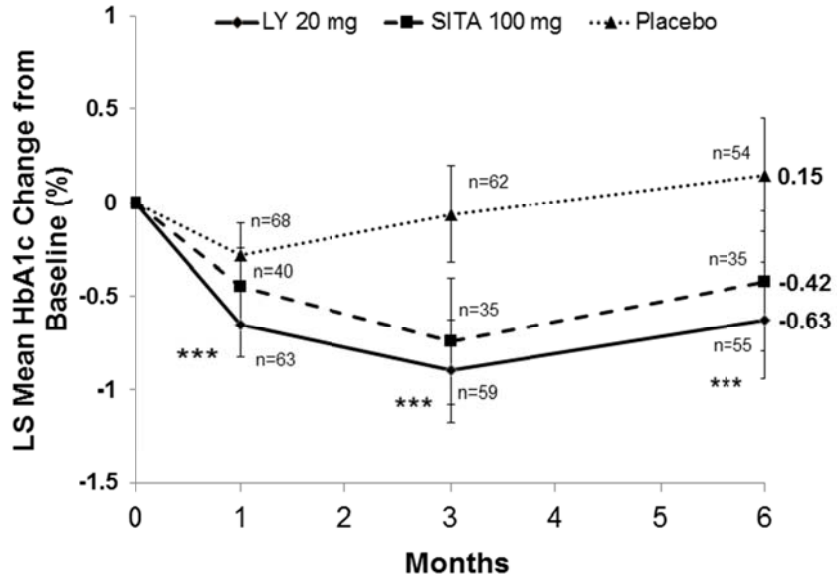
Figure 3. HbA1c: Change from Baseline to Month 6[a]



***p<0.001 LY vs. placebo; LY vs. sitagliptin: p=0.048 at Month 1

HbA1c, %	LY2409021		Sitagliptin		Placebo	
	n	mean (SD)	n	mean (SD)	n	mean (SD)
Baseline	65	8.12 (0.98)	41	8.25 (0.91)	68	8.26 (0.86)
Month 6	55	7.64 (1.23)	35	7.89 (0.85)	54	8.49 (1.47)
Month 12	16	7.00 (0.64)	7	7.93 (0.48)	11	7.45 (0.85)

[a] The primary endpoint of the study was Month 6.

Abbreviations: HbA1c = hemoglobin A1c; LS = least square; LY = LY2409021; n = number of patients; SD = standard deviation; SITA = sitagliptin.

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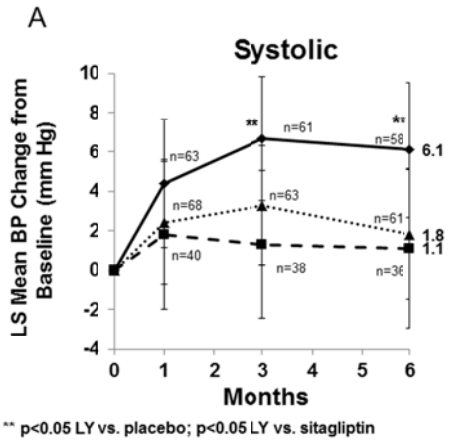
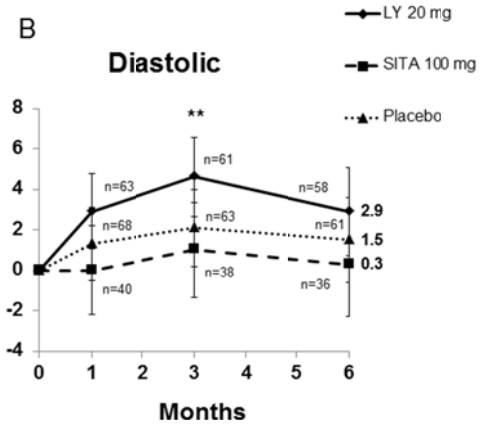
Figure 4. Systolic (A) and Diastolic (B) Blood Pressure: Change from Baseline to Month 6[a]



** p<0.05 LY vs. placebo; p<0.05 LY vs. sitagliptin

SBP, mm Hg	LY2409021		Sitagliptin		Placebo	
	n	mean (SD)	n	mean (SD)	n	mean (SD)
Baseline	65	126 (13)	41	128 (11)	68	126 (12)
Month 6	58	131 (14)	36	127 (12)	61	126 (14)
Month 12	23	125 (11)	15	124 (15)	19	128 (13)
4 months posttreatment	57	127 (11)	36	127 (13)	57	126 (11)



** p<0.05 LY vs. sitagliptin at Months 1 and 3 and LY vs. placebo at Month 3

DBP, mm Hg	LY2409021		Sitagliptin		Placebo	
	n	mean (SD)	n	mean (SD)	n	mean (SD)
Baseline	65	77 (7)	41	76 (7)	68	76 (8)
Month 6	58	78 (9)	36	75 (6)	61	76 (8)
Month 12	23	76 (8)	15	76 (10)	19	77 (7)
4 months posttreatment	57	77 (8)	36	75 (9)	57	76 (7)

[a] The primary endpoint of the study was Month 6.

Note: blood pressure calculated as mean of 3 readings.

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Abbreviations: BP = blood pressure; DBP = diastolic blood pressure; LS = least square; LY = LY2409021; n = number of patients; SBP = systolic blood pressure; SD = standard deviation; SITA = sitagliptin.

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